FILE 'BIOSIS, MEDLINE, EMBASE, EMBAL, SCISEARCH, BIOTECHDS, CAPLUS' ENTERED AT 02:53:57 ON 28 JUN 2002

L1 207 S **COMPUTER** AND **DESIGN** AND **GEOMETRIC** AND **STRUCTURE**

L2 9 S L1 AND (**HYDROPH**?)

L3 5 DUP REM L2 (4 DUPLICATES REMOVED)

L4 2 S L1 AND (**SEARCH**? () **DATABASE**?)

L5 2 S L4 NOT L3

L6 2 DUP REM L5 (0 DUPLICATES REMOVED)

L3 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:286494 CAPLUS

DOCUMENT NUMBER: 133:68365

TITLE: Benzodiazepine-induced hyperphagia: development and assessment of a 3D pharmacophore by computational methods

AUTHOR(S): Filizola, Marta; Harris, Danni L.; Loew, Gilda H.

CORPORATE SOURCE: Molecular **Research** Institute, Mountain View, CA, 94043, USA

SOURCE: Journal of Biomolecular **Structure** & Dynamics (2000), 17(5), 769-778
CODEN: JBSDD6; ISSN: 0739-1102

PUBLISHER: Adenine Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Benzodiazepine receptor (BDZR) ligands are structurally diverse compds. that bind to specific binding sites on GABAA receptors and allosterically modulate the effect of GABA on chloride ion flux. The binding of BDZR ligands to this receptor system results in activity at multiple behavioral endpoints, including anxiolytic, sedative, anticonvulsant, and hyperphagic effects. In the work presented here, a computational procedure developed in our lab. has been used to obtain a 3D pharmacophore for ligand recognition of the GABAA/BDZRs initiating the hyperphagic response. To accomplish this goal, 17 structurally diverse compds., previously assessed in our lab. for activity at the hyperphagic endpoint, were used. The result is a four-component 3D pharmacophore. It consists of two proton acceptor atoms, the centroid of an arom. ring and the centroid of a **hydroph**obic moiety in a common **geometric** arrangement in all compds. with activity at this endpoint. This 3D pharmacophore was then assessed and successfully validated using three different tests. First, two BDZR ligands, which were included as neg. controls in the set of seventeen compds. used for the pharmacophore development, did not fit the pharmacophore. Second, some benzodiazepine ligands known to have activity at the hyperphagia endpoint, but not included in the pharmacophore development, were used as pos. controls and were found to fit the pharmacophore. Finally, using the 3D pharmacophore developed in

the present work to **search** 3D **database**s, over 50 classical benzodiazepines were found. Among them, were benzodiazepine ligands known to have an effect at the hyperphagic endpoint. In addn., the novel compds. also found in this **search** are promising therapeutic agents that could beneficially affect feeding behavior.

L3 ANSWER 2 OF 5 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 1
ACCESSION NUMBER: 1996:327189 BIOSIS
DOCUMENT NUMBER: PREV199699049545
TITLE: Controlling topology and native-like behavior of de Novo-**design**ed peptides: **Design** and characterization of antiparallel four-stranded coiled coils.
AUTHOR(S): Betz, Stephen F.; Degrado, William F. (1)
CORPORATE SOURCE: (1) Johnson Res. Foundation, Dep. Biochem. Biophys., Univ. Pennsylvania, Philadelphia, PA 19104-6059 USA
SOURCE: Biochemistry, (1996) Vol. 35, No. 21, pp. 6955-6962. ISSN: 0006-2960.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The de novo **design** of peptides and proteins has emerged as an attractive approach for investigating protein **structure** and function. Here, the **design**, synthesis, and characterization of a new series of alpha-helical peptides intended to form antiparallel four-stranded coiled coils is described. **Computer** models were generated without the use of extant protein **structure**s and were used to refine the sequence. The peptides are of the general formula Ncap-(X-aZ-bZ-cL-dZ-eZ-fZ-g)-3-Ccap, where X is either Ala, Val, Thr, or Leu, and Ncap and Ccap are sequences **design**ed to satisfy the helices unpaired amide nitrogens and carbonyl oxygens, respectively. The **hydroph**obic residues (at positions a and d) were chosen so that **geometric** packing of large and small **hydroph**obes would favor an antiparallel arrangement. Special attention was also given to residues at the helix-helix interfaces. These residues were chosen to balance potential attractive and repulsive electrostatic forces so that the desired topology was favored while other possible folds were destabilized. Two of the four peptides associate under neutral conditions into the desired tetramers. One of the complexes (a = Val) behaves like a native-like protein as judged by NMR, thermodynamics, and apolar dye (ANS) binding. The other tetrameric complex (a = Leu) exhibits broader NMR resonances, diminished values of DELTA-H and DELTA-C-p, and tight binding of the **hydroph**obic dye ANS, similar to early **design**ed proteins. These results reinforce the importance of optimizing van der Waals packing interactions in protein **design** but demonstrate that **hydroph**obic packing must be balanced with hydrogen-bonding and

electrostatic interactions to produce novel native-like proteins.

L3 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:45388 CAPLUS
DOCUMENT NUMBER: 124:169926
TITLE: WPDB-PC Windows-based interrogation of macromolecular **structure**
AUTHOR(S): Shindyalov, Ilya N.; Bourne, Philip E.
CORPORATE SOURCE: Department Biochemistry Molecular Biophysics, Columbia University, New York, NY, 10032, USA
SOURCE: J. Appl. Crystallogr. (1995), 28(6), 847-52
CODEN: JACGAR; ISSN: 0021-8898
DOCUMENT TYPE: Journal
LANGUAGE: English
AB WPDB version 2.0 is a Microsoft-Windows-based program for browsing and interrogating native and derived structural features of biol. macromols. using data obtained from the Protein Data Bank (PDB). Major features of WPDB are a 20-fold compression of PDB files and query and anal. tools. The latter permit the **geometric** and sequence properties of **structures** to be analyzed individually or through comparative anal. The object-oriented software **design** provides a high level of interaction between display windows, which facilitates information discovery. Three examples are given to illustrate the capabilities of the software, namely: location of the distribution of the most **hydroph**obic residues in the acid proteases; exploration of the **geometric** features of a 4-helix bundle motif; and examn. of the effect of antibody binding by comparison of a neuraminidase with a neuraminidase-antibody complex. Addnl. details are available to World Wide Web (WWW) users at the URL http://www.sdsc.edu/CCMS/Packages/wpdb.htm
1.

L3 ANSWER 4 OF 5 MEDLINE
ACCESSION NUMBER: 89199601 MEDLINE
DOCUMENT NUMBER: 89199601 PubMed ID: 2539476
TITLE: Analysis of the in vitro antiviral activity of certain ribonucleosides against parainfluenza virus using a novel **computer** aided receptor modeling procedure.
AUTHOR: Ghose A K; Crippen G M; Revankar G R; McKernan P A; Smee D F; Robins R K
CORPORATE SOURCE: Nucleic Acid **Research** Institute, Costa Mesa, California 92626.
CONTRACT NUMBER: GM 37123 (NIGMS)
SOURCE: JOURNAL OF MEDICINAL CHEMISTRY, (1989 Apr) 32 (4) 746-56.

Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198905
ENTRY DATE: Entered STN: 19900306
Last Updated on STN: 19970203
Entered Medline: 19890515

AB The in vitro antiviral activity of 28 nucleosides against the parainfluenza virus type 3 has been analyzed by using a novel **computer** aided receptor modeling procedure. The method involves an extensive modification of our earlier work (Ghose, A. K.; Crippen, G. M. J. Med. Chem. 1985, 28, 333). It presents a more straightforward algorithm for the steps that suffered from subjectivity in the earlier method. The method first determines the possible low-energy conformations of the nucleosides, and assigns a priority value for each conformation of each molecule. It then performs the following steps repeatedly, until it finds an acceptable solution. Starting from the conformation of highest priority, the various energetically allowed conformations of the other molecules are superimposed on it. On the basis of the physicochemical property matching (or overlapping), the best superposition is determined. The superimposed molecules are dissected into a minimum number of parts and the local physicochemical properties at different regions are correlated with their binding data (antiviral activity). A modified version of distance **geometry** has been used for **geometric** comparison of the **structure** of the molecules. On the basis of the virus rating (VR) of 28 ribonucleosides, this procedure hypothesized the minimum-energy conformation of 6-(methylthio)-9-beta-D-ribofuranosylpurine as a reference conformation and used three physicochemical properties, namely **hydroph**obicity, molar refractivity, and formal charge density for property matching. The binding-site cavity was divided into seven regions or pockets to differentiate the nature of interaction quantitatively. The model suggests that the 2- and 3-positions of the purine ring and the corresponding atoms of the other rings get some steric repulsion, and nucleosides having a single five-membered heterocyclic ring will better fit this virus. The methylthio group gets a strong attraction from dispersive interaction. Both **hydroph**ilic and dispersive groups are attractive here. Although our calculation supports the previously suggested active conformation of ribavirin, it shows that it is not the global minimum-energy conformation. The difference lies in the orientation of the amide group. The calculated viral rating from this model showed a correlation coefficient of 0.971 with the observed values, and the explained variance and the standard deviation of the fit were 0.880 and 0.125, respectively.

L3 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1989:434696 CAPLUS
DOCUMENT NUMBER: 111:34696
TITLE: **Computer** based method for protein engineering
INVENTOR(S): Pantoliano, Michael W.; Ladner, Robert Charles
PATENT ASSIGNEE(S): Genex Corp., USA
SOURCE: PCT Int. Appl., 79 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 8808165	A1	19881020	WO 1988-US850	19880318
W: DK, JP				
RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE				
US 4853871	A	19890801	US 1987-34966	19870406
PRIORITY APPLN. INFO.:			US 1987-34966	19870406

AB A **computer**-based method and app. for identifying sites in a protein which can be converted to cysteine residues to create a potentially protein-stabilizing disulfide bond is described. A central processing unit (CPU) is connected to a massbus which connects the CPU to storage devices which store the **database** contg. the amino acid sequences and the application software package. A **computer**-generated graphics system receives images from the CPU to be displayed. The display allows an expert operator to view each potentially protein-stabilizing disulfide bond and rank them from most likely to stabilize an engineered protein to those least likely to stabilize it. The method comprises (1) examg. each selected pair of amino acid residues to det. if they contain certain atoms whose relative 3D positions possess a **geometric** conformation similar to the corresponding atoms of a known disulfide bridge; (2) examg. amino acid pairs identified in step 1 to det. if the new atoms of a possible disulfide linkage can be accommodated without creating unacceptable hindrance; (3) permitting the expert operator to view the sites which can accommodate the disulfide bridge without altering the tertiary **structure** of the protein and to rank the sites; and (4) evaluating the ranked sites according to expert rule criteria (e.g. Would evolutionarily conserved amino acids be lost. Would formation of the linkage result in loss of favorable **hydroph**obic interactions). The method was successfully applied in introducing stabilizing disulfide bonds into subtilisin BPN'.

L6 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1992:425570 CAPLUS
DOCUMENT NUMBER: 117:25570
TITLE: 3D **database search**ing in drug **design**
AUTHOR(S): Martin, Yvonne C.
CORPORATE SOURCE: Pharm. Prod. Div., Abbott Lab., Abbott Park, IL, 60064, USA
SOURCE: J. Med. Chem. (1992), 35(12), 2145-54
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Three-dimensional (3D) **search**ing programs test thousands of chem. **structure**s for a match of 3D criteria. Such programs have been used to **design** new bioactive mols. and to recognize new biol. properties in known mols. The 3D **search** criteria may be derived from an exptl. 3D **structure** of a macromol. binding site or from mol. modeling of ligands. The programs **search databases** of **structures** derived from crystallog. observations or theor. calcns. Alternatively, they may generate the 3D **structure** as part of the **search** process. Various available **search**ing strategies emphasize **geometric** or shape characteristics of the mols. identified. Programs that **design** mols. to match 3D criteria are a related area of active re**search**. The investigation of strategies for examn. of all possible conformations of the mols. is a 2nd area of active re**search**. Others are evaluating strategies to make the **search**es more efficient. Thus, 3D **search**ing is possible today and will be more powerful in the future.

L6 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1991:80616 CAPLUS
DOCUMENT NUMBER: 114:80616
TITLE: **Computer design** of potentially bioactive molecules by **geometric search**ing with ALADDIN
AUTHOR(S): Martin, Yvonne C.
CORPORATE SOURCE: Comput. Assisted Mol. Des. Proj., Abbott Lab., Abbott Park, IL, 60064, USA
SOURCE: Tetrahedron Comput. Methodol. (1990), 3(1), 15-25
CODEN: TCMTE6; ISSN: 0898-5529
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Structurally novel potential dopamine agonists were **design**ed by **search**ing **database**s of 3-dimensional (3D) **structure**s to find templates that match **geometric** criteria and can be modified into mols. suggested for synthesis. A **search** of 3D **structure**s (54,296) from 3 different **database**s generated 499 structurally unique mols. that

meet the **geometric** criteria for D-2 dopaminergic activity. The **search** identified 8 of 9 classes of known fused ring phenolic dopaminergic compds. and 62 other classes of fused ring compds. with potential activity. The low obsd. frequency of finding the same ring class more than once suggests that addnl. **search**es will **design** many addnl. mols. Compd. **design** based on 3D sub**structure search**ing methods appears to be equally applicable to suggesting new classes of compds. for beginning or for mature medicinal chem. investigations and does not require the construction of special libraries of templates.